PATENT COOPERATION TREATY

PCT

REC'D 19 MAY 2006

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

PCT

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference X-16115	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/US2005/005418	International filing date *(day/month/year)* 18.02.2005	Priority date *(day/month/year)* 25.02.2004

International Patent Classification (IPC) or national classification and IPC
INV. C07D223/16 C07D401/12 C07D417/12 C07D413/12 C07D403/12 C07D409/12 C07D405/12 C07D413/14 C07D417/06 C07D403/06 A61K31/55 A61P25/22 A61P25/24 A61P25/30 A61P3/04

Applicant
ELI LILLY AND COMPANY

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 7 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 15 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
20.12.2005	19.05.2006

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US2005/005418

Box No. I Basis of the report

1. With regard to the **language**, this report is based on

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3(a) and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4(a))
   - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-574 as originally filed

   Claims, Numbers

   1-37 filed with telefax on 20.12.2005

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 18-25 (with respect to industrial applicability)

because:

☒ the said international application, or the said claims Nos. 18-25 relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*.

☐ no international search report has been established for the said claims Nos.

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b) and 13*ter*.2.

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-37
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-37
Industrial applicability (IA)	Yes:	Claims	1-17,26-37
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 18-25 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: WO 93/04686 A (SMITHKLINE BEECHAM CORPORATION) 18 March 1993 (1993-03-18)

D2: US-A-4 265 890 (HOLDEN ET AL) 5 May 1981 (1981-05-05)

D3: WO 93/03015 A (SMITHKLINE BEECHAM CORPORATION) 18 February 1993 (1993-02-18)

D4: KILPATRICK, ANDREW T. ET AL: "The .alpha.2-adrenoceptor antagonist SK & F 104078 has high affinity for 5-HT1A and 5-HT2 receptors" EUROPEAN JOURNAL OF PHARMACOLOGY , 166(2), 315-18 CODEN: EJPHAZ; ISSN: 0014-2999, 1989, XP002328505

V.1. Novelty:

The compounds according to the general formula (I) of claim 1 have not been disclosed in the available prior art. Therefore, the subject-matter of claims 1-37 is novel (Article 33(2) PCT).

V.2. Inventive Step:

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-37, in as far as novel, does not involve an inventive step in the sense of Article 33(3) PCT:

Documents D1 and D3 disclose general formulae which overlap with the present formula I. The compounds of D1 and D3 are adrenergic antagonists and useful for the treatment of depression and obesity.

Even though the compounds of D1 and D3 are characterized as α-adrenoceptor antagonists, whereas the present compounds embody 5-HT_{2C} receptor agonists, it is known from D4 that the benzazepine derivative SK&F 104078 which is in principle an α_2-adrenoceptor antagonist, has high affinity for 5-HT_2 receptors.

In view of the teaching of the prior art, it would have been obvious to the skilled person to associate the formulae of D1 and D3 with a 5-HT_2 receptor activity, and to choose among said formulae when looking for further compounds for the treatment of obesity and neurological disorders such as depression.

Applicant argues that the present compounds are selective 5-HT_{2C} receptor agonists, particularly against adrenergic and dopaminergic receptors, thereby avoiding undesirable adverse events and cross reactivity associated with current therapies.

Such as selectivity can indeed be regarded as an indication for inventive step.

Hence, the technical problem underlying the present invention can be formulated as the provision of further compounds for the treatment of obesity, obsessive compulsive disorders, depression, anxiety, sleep disorders which are selective 5-HT_{2C} receptor agonists.

However, an inventive step relying on such an effect requires evidence to this effect, e.g. by means of comparative tests which convincingly show that the effect has its origin in the distinguishing feature of the invention over the prior art.

In absence of comparative tests with the prior art, the selectivity referred to by the applicant has therefore not been properly demonstrated in the description. Such alleged but unsupported advantages cannot be taken into consideration in respect of the determination of the problem underlying the application and hence the assessment of inventive step.

Consequently, the objective technical problem is merely to provide further compounds for the treatment of obesity, obsessive compulsive disorders, depression, anxiety, sleep disorders.

The arbitrary selection of substituents from the general formulae disclosed in D1 and D3 is one of several straightforward possibilities at which the skilled person would arrive without the exercise of inventive skill, in order to solve the problem posed.

Therefore, the subject-matter of claims 1-37 cannot be considered as involving an inventive step (Article 33(3) PCT).

V.3. Industrial Applicability:

The present application relates to compounds which are useful for the treatment of obesity, obsessive compulsive disorder, depression and anxiety and the subject matter of claims 1-17, 26-37 is therefore considered as industrially applicable (Article 33(4) PCT).

For the assessment of the present claims 18-25 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.